REMARKS

Claims 1-11 and 13-30 are pending in this application and have been rejected by the Examiner. Claim 12 has previously been canceled. Claims 15-30 have been withdrawn. Claims 1-11 and 13-14 have been amended to remove the non-elected invention and for clarification. Claim 11 has been amended to remove the language "pharmaceutically acceptable salts or prodrugs thereof" since "in free, pharmaceutically acceptable salt or prodrug form" language has already been included by virtue of claim 11's dependency on claim 1. It is believed no new matter has been added.

Restriction Requirement

Previously, the Examiner restricted the claims thirteen ways, arguing that U.S. Patent 4,639,436 (Junge et al.) anticipates the claimed compounds of Group I and therefore does not meet the unity of invention requirement. *Office Action* dated 7/28/2008, p. 4. In response, Applicants argued that Junge et al. is not anticipatory because Junge et al. does not disclose a compound having the same stereochemical configuration as in the claimed invention. In response, the Examiner argued that the structural formula of the compounds of the current invention includes the dotted ("----") and the wedged ("▬") configurations, which allegedly denotes the up and down configuration from the ring, rather than the well recognized "R" and "S" configuration and therefore does not limit the claimed compounds to a specific stereochemistry. *Office Action* dated 12/8/2009, p. 2. The Examiner, therefore, concluded that the claims are without stereo limitations and as such are anticipated by Junge et al.

Applicants respectfully disagree. It is well known in the chemical art that the use of a solid wedge depicts a bond projecting from the paper towards the reader, while the dash wedge (or dash line) depicts a bond projecting from the paper away the reader. *See "Organic Chemistry"* Francis A. Carey, p. 28 (2nd Edition, McGraw-Hill, Inc., 1992). It is also well known that the absolute stereochemistry (R) or (S) of a compound may be determined by the well-known Cahn-Ingold-Prelog Notation System using a two step procedure wherein (1) the four substituents on the chiral carbon are prioritized using the well-known Sequence Rule and (2) the configuration

(R) or (S) is assigned based on the clockwise or counter-clockwise direction (respectively) of the atoms when the four substituents are observed with the lowest priority atom directed away from the reader and going from the highest priority substituent to the lowest priority substituent (i.e., in the order of decreasing precedence of the three highest-ranked substituents). *See* "*Organic Chemistry*" Robert Thornton Morrison and Robert Neilson Boyd, p. 138-141 (5th Edition Allyn and Bacon, Inc. 1987); *See also* "*Organic Chemistry*" Francis A. Carey, p. 269, Table 7.1 (2nd Edition, McGraw-Hill, Inc. 1992). Specifically, Francis A Carey states:

> Compounds in which a stereogenic center is part of a ring are handled in an analogous fashion. To determine, for example, whether the configuration of (+)-4-methylcyclohexene is *R* or *S*, treat the right- and left-hand paths around the ring as if they were independent substituents. Orienting the molecule with the hydrogen directed away from us, we see that the order of decreasing sequence rule priority is clockwise. The absolute configuration is *R*.

"*Organic Chemistry*" Francis A. Carey, p. 271 (2nd Edition, McGraw-Hill, Inc. 1992). Therefore, given a structural formula with the solid wedge and dash line notation, one skilled in the art will immediately appreciate the stereochemical configuration of that compound. In the present case, one skilled in the art will immediately appreciate that the claimed compounds of the invention as drawn depict a specific stereochemistry and not compounds without stereo limitation. Junge et al., on the other hand, discloses desoxynojirimycin compounds and therefore does not disclose a compound having the same stereochemical configuration as the claimed invention. As such, Junge et al. does not anticipate the current claims. Accordingly, the claims provide a contribution over the art and therefore, satisfy the unity of invention requirement. Applicants again respectfully request the Examiner to reconsider and withdraw the finality of the restriction requirement.

Rejection under 35 *U.S.C.* § 112, Second Paragraph

The Examiner rejected claims 1-10 and 13-14 for being indefinite, arguing that the doted and wedge notation does not offer any stereo limitation. Applicants respectfully disagree. MPEP 2173.05(t) provides that "[c]laims to chemical compounds and compositions containing chemical compounds often use formulas that depict the chemical structure of the compound. These structures should not be considered indefinite nor speculative in the absence of evidence that the assigned formula is in error." Here, the Examiner did not argue that the structure is in error, but

that the structure did not specify the stereo limitation. To this point, MPEP 2173.02 provides that "a claim term . . . is not indefinite if the meaning of the claim term is discernible." *Id.* citing *Bancorp Services, L.L.C. v. Hartford Life Ins. Co.*, 359 F.3d 1367, 1372, 69 USPQ2d 1996, 1999-2000 (Fed. Cir. 2004) (holding that the disputed claim term "surrender value protected investment credits" which was not defined or used in the specification was discernible and hence not indefinite because "the components of the term have well recognized meanings, which allow the reader to infer the meaning of the entire phrase with reasonable confidence"). As previously argued in the restriction requirement section above, the solid wedge and dash configuration is well understood and commonly used in the chemical art. The Cahn-Ingold-Prelog Notation System may be used to determine the (R) and (S) configuration for compounds having stereogenic center as part of a ring as for non-cyclic structures (see arguments above). By looking at the chemical structure with the solid and dash wedge configuration, a configuration which is well-recognized in the art, a skilled artisan will immediately appreciate the stereochemistry limitation of the compounds and the boundaries of the claims with reasonable confidence. As such, Applicants respectfully submit that the rejection under Section 112, Second Paragraph is improper. Withdrawal of the rejections under this section is earnestly requested.

Rejection under 35 *U.S.C.* § 112, First Paragraph

The Examiner rejected claims 1-11 and 13-14 for failing to comply with the enablement requirement, arguing that the specification does not provide "sufficient information as to what kind of modification of the drug functional groups to provide an inactive prodrug which will be released into the active form in vivo." *Office Action* dated 12/8/2008, p. 3. Applicants respectfully disagree. Page 5, paragraph [0096] of the published specification (2006/011400) provides that "[s]uitable prodrugs of the compounds of formula (I) include, but are not limited to, pharmaceutically acceptable esters such as C_{1-6} alkyl esters." As such, the specification enables one skilled in the art to make and use C_{1-6} alkyl esters of formula (I) as a prodrug without undue experimentation. In view of these comments, Applicants respectfully request the Examiner to reconsider and withdraw the rejection under Section 112, First Paragraph.

Rejection under 35 *U.S.C.* § 102(b)

The Examiner rejected claims 1-11 and 13-14 for being anticipated by Boeshagen et al. CA 113:126581; Ezure et al. CA 116:236093, RN 141206-38-4; Broek et al. CA 119:96007, RN 149302-52-3, RN 149302-53-4; Berg et al. RN 8117-43-3; Kurihara et al. CA 114:185939 RN 1333342-47-9, under 35 *U.S.C.* § 102(b) based on the conclusion that the claimed compounds do not contain any stereo limitation. *Office Action* dated 12/8/2008, p. 2-3. As argued in the Restriction Requirement and Indefiniteness sections above, the solid wedge and dash (wedge/line) configuration is well understood and commonly used in the chemical art. The Cahn-Ingold-Prelog Notation System may be used for compounds having stereogenic center as part of a ring as for non-cyclic structures (see arguments above). In looking at the chemical structure of the claimed compounds, one skilled in the art will immediately appreciate the stereo limitation of the compound (i.e., (2S, 3S, 4R, 5S)) with reasonable confidence. Boeschagen et al., CA 113:126581; Broek et al., CA 119:96007; Kurihara et al., CA 114:185939 and Berg et al., CA 96:117597 (the search results cited by the Examiner) all disclose compounds having a (2R, 3R, 4R, 5S) configuration, and Ezure et al., CA 116:236093 discloses compounds having a (2R, 3S, 4R, 5S) configuration, all of which differ from the (2S, 3S, 4R, 5S) stereo limitation of the claimed invention. It is well established that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Because none of these compounds have the stereo limitation of the claimed invention, they fail to anticipate the claimed invention. Reconsideration and withdrawal of the rejections under Section 102 is respectfully requested.

Rejection under 35 *U.S.C.* § 103

The Examiner rejected Claims 1-11 and 13-14 under 35 *U.S.C.* § 103(a) as allegedly being obvious over Boeshagen et al. CA 113:126581; Ezure et al. CA 116:236093, RN 141206-38-4; Broek et al. CA 119:96007, RN 149302-52-3, RN 149302-53-4; Berg et al. RN 8117-43-3; Kurihara et al. CA 114:185939 RN 1333342-47-9 in view of U.S. Patent 5,051,407, U.S. Patent 7,256,005 and Kato et al. The Examiner argued that Boeshagen et al. CA 113:126581; Ezure et al. CA 116:236093; Broek et al. CA 119:96007; Berg et al. and Kurihara et al. CA 114:185939

disclose biological active hydroxymethyl-piperidinyltriol compounds having the same molecular formula as the claimed invention and that based on the generic formula disclosed in U.S. 5,051,407 ('407) and EP 536, 402 ('402), these references disclose that all variations of stereo arrangements are biologically active. Although the Examiner stated that the '407 and '402 references explicitly recognize that all enantiomers of the triols are active and the activity only differ by degree, the Examiner did not point out where in the references this statement is disclosed. The Examiner further argued that "modification of one enantiomer to another is a routine skill to one in the field" as evidenced by Kato et al., *J. Med. Chem.* (2005) 48:2036-2044 (Kato et al.). Furthermore, as U.S. 7,256,005 allegedly teaches "the variation of active stereo modification" and Kato et al. teaches that such variations are biologically active, the Examiner concluded that one of ordinary skill in the art would be motivated to prepare all enantiomers with the expectation that all compounds are active and some may be better or more selective then others. As such, the Examiner concluded that preparation of stereo-isomer is prima facie obvious in absence of unexpected results.

Applicants respectfully disagree. As argued in the anticipation section above, Boeschagen et al., CA 113:126581; Broek et al., CA 119:96007; Kurihara et al., CA 114:185939, Berg et al., CA 96:117597 and Ezure et al., CA 116:236093 all disclose compounds having a different stereochemical configuration from the (2S, 3S, 4R, 5S) configuration of the claimed invention. While U.S. 5,051,407 and EP 0 536 402 both disclose 3,4,5-trihydroxypiperidine derivatives and specifically disclose desoxynorijimycin and deoxygalactostatin, respectively, these compounds also differ in stereochemical configuration from the claimed invention. Applicants are not able to locate in these references an explicit teaching that all enantiomers are active and that the activities differ only by degree, as asserted by the Examiner. In fact, an article published in 2003 (after the priority date of the current application) by Butters et al. "Therapeutic Applications of Imino Sugars in Lysosomal Storage Disorders", *Current Topics in Medicinal Chemistry* (2003) 3:561-674, shows that the activities of different imino sugars are unpredictable. Table 1 of Butters et al. shows that deoxynojirimycin (DNJ) is not only ten times less potent against ceramide-specific glucosyltransferase than its stereoisomer deoxygalactojirimycin (DGJ), but also at least 1,000-3,700 times more active against α-glucosidase I, which activity is known to cause

undesirable side effects. *Id.* at p.563, Table 1. As such, Applicants respectfully submit that the activities of the different enantiomers of hydroxymethyl-piperidinyltriol derivatives are unpredictable and that one skilled in the art, in knowing the activity of one enantiomer, would not be motivated to test the other enantiomer as there would not be an expectation of success. This conclusion is in agreement with the holding of the recent Federal Circuit case, *Sanofi- Synthelabo v. Apotex*, WL 5191848 (Fed. Cir. Dec. 12, 2008), where the Court found that the dextrorotatory enantiomer of methyl alpha- 5(4,5,6,7-tetrahydro(3,2-c) thienopyridyl)(2-chlorophenyl)-acetate, which possesses "all of the favorable antiplatelet activity but with no significant neurotoxicity" is unobvious over the levorotarory enantiomer, which possesses "no antiplatelet activity but virtually all of the neurotoxicity". Accordingly, the disclosure of the activity and/or toxicity of one enantiomer would not render obvious the activity and/or toxicity of another enantiomer.

The Examiner also argued that Kato et al. teaches that variations of the enantiomers are biologically active and that one skilled in the art would be motivated to prepare all enantiomers with the expectation that all compounds are active. Applicants respectfully disagree. Firstly, Kato et al. is not prior art to the claimed invention. Kato et al. was published on the Web on September 18, 2004. The current application is a national phase application under 35 U.S.C. 371 of PCT/GB2003/003244, which PCT application was filed on July 17, 2003, claiming priority back to July 17, 2002. PCT Article 11(3) provides that "...an international filing date shall have the effect of a regular national application in each designated State as of the international filing date, which date shall be considered to be the actual filing date in each designated State". As such, the effective filing date of the current application is July 17, 2003 and Kato et al. is not available as prior art.

While Kato et al. is not prior art to the current invention, it nevertheless shows, as in Butters et al., that there is no predictability for the inhibitory activities of different enantiomers of hydroxypiperidine compounds. Tables 3 of the Kato article shows that the dextrorotarory enantiomer of deoxynojirimycin (D-DNJ) is active against human α- and β-glucosidase, but not active against human α- or β-mannosidase, α- or β-galactosidase, and α-fucosidase. On the other hand, D-*allo*-DNJ is not active against any of the listed human enzymes, but the L-*allo*-DNJ is active against human α-mannosidase. Similarly, D-*ido*-DNJ is active against human β-glucosidase

and α-galactosidase, but L-*ido*-DNJ is not active against any of the enzymes listed in the article. Applicants, therefore, respectfully submit that even with hindsight, it is difficult to rationalize the inhibitory activities of the various enantiomers of hydroxymethyl-piperidinyltriol derivatives. Given the unpredictability of the activities of sugar and sugar mimetic compounds (i.e., hydroxymethyl-piperidinyltriol), one skilled in the art would not expect that all of the stereoisomers are active against a specific enzymer and therefore would not be motivated to isolate and test each compound and still have an expectation of success as asserted by the Examiner.

Although U.S. Patent 7,256,005 ('005) discloses a compound having the same configuration as the claimed compounds, Applicants note that this reference is also not prior art to the invention. MPEP 2106.03 provides that "subject matter relied upon in the rejection must be disclosed in the earlier-filed application in compliance with 35 U.S.C. 112, first paragraph, in order to give that subject matter the benefit of the earlier filing date under 35 U.S.C. 102(e)." Here, the '005 patent was filed (September 23, 2003) after the current invention's effective filing date (July 17, 2003). The '005 patent claims priority to three provisional applications and a PCT application (PCT/US00/21732) and therefore may qualify as a 102(e) prior art. Even though the earliest priority date of the '005 patent is August 10, 1999, the (2S, 3S, 4R, 5S) arylalkyl substituted hydroxymethyl-piperidinyltriol compound was not disclosed in Provisional application number 60/198,621 (filed April 20, 2000), provisional application number 60/148,101 (filed August 10, 1999) and PCT/US00/21732 (filed August 10, 2000). These priority applications, while disclosing the (2S, 3S, 4R, 5S) hydroxymethyl-piperidinyltriol compounds, focused on long N-alkyl chain derivative of trihydroxypiperidine, e.g., C_{8-16}alkyl, particularly C_9alkyl, as antiviral agents. The arylalkyl substituted trihydroxypiperidine subject matter was not introduced until the filing of provisional application number 60/412,560 on September 23, 2002. As the subject matter of the '005 patent relied on by the Examiner to reject the current claimed invention (i.e., arylalkyl substituted (2S, 3S, 4R, 5S) compounds) is not disclosed in the earlier priority applications, such subject matter does not afford the earlier priority dates. The '005 patent at most would have a priority date of September 2003 (if at all). The current application, on the other hand, claims priority back to July 17, 2002, which predates provisional application 60/412,560. As such, the '005 patent, to the extent that the Examiner relied on the arylalkyl substituted

hydroxymethyl-piperidinyltriol subject matter, is not prior art to the claimed invention.

While it is true that the priority applications of the '005 application discloses the long chain alkyl substituted (2S, 3S, 4R, 5S) hydroxypiperidine derivatives, this prior art reference does not render the claimed compounds useful as GCS inhibitors obvious. In fact, the priority applications of the '005 patent teaches away from the claimed invention. For instance, the priority applications of the '005 patent, WO 01/10429 (PCT/US00/21732) and U.S. Provisional Appl. No. 60/198,621, disclose the following:

> [t]he nitrogen-containing virus-inhibiting compound can be administered to a cell or an individual affected by a virus. The compound can inhibit morphogenesis of the virus, or it can treat the individual . . . For example, the N-nonyl, N-decyl, N-3-oxa-nonyl, N-3-oxa-decyl, N-7-oxa-nonyl, N-7-oxa-decyl compounds are antiviral. The antiviral activity is substantially unrelated to the remaining functionalities of the compound . . .
>
> . . . Long chain N-alkyl compounds are agents that exhibit an inhibitory effect on viral expression. While certain short chain N-alkyl derivatives of imino sugars (e.g., N-butyl DNJ) are potent inhibitors of the N-linked oligosaccharide processing enzymes, such as α-glucosidase I and α-glucosidase II . . . Some long chain N-alkyl compounds of the invention may exhibit substantially little or no inhibition of a glycosidase enzyme, especially in comparison with N-butyl DNJ or N-nonyl DNJ. . . . For example, the nitrogen-containing virus-inhibiting compound can have an IC_{50} of about 10μM or less, preferably 3μM or less, for the inhibition of BVDV or another virus, but the same compounds may exhibit little activity against glycosidases or inhibition of glycolipid synthesis.

WO 01/10429, p. 12, lines 26-30, p. 13, lines 15-26 (*emphasis added)*; *See Id.* at p. 25, Table 2; *See also* U.S. Prov. Appl. No. 60/198,621, p.11, lines 10-15 and p. 12, lines 1-12. As such, these applications claimed a broad class of nitrogen-containing virus-inhibiting compound which includes an N-C_{8-16}alkyl group. In reading this, one skilled in the art would conclude that the activity is substantially unrelated to the trihydroxypiperidine core and that a shorter alkyl chain substitution would be desirable for glycolipid synthesis inhibitors rather the long, bulky arylalkyl groups as claimed in the current invention. This teaching would therefore, discourage a skilled artisan from modifying the nitrogen-containing compounds of the '005 patent to arrive at the currently claimed compounds and expect them to have GCS inhibitory activities. As such, it is respectfully submitted that the prior art cited would not only not render the claimed invention

obvious, but also teaches away from the current invention. In light of the comments herewith, Applicants respectfully request withdrawal of the rejections of claims 1-11 and 13-14 under 35 U.S.C. Section 103(a).

Provisional Obviousness Type Double Patenting Rejection

The Examiner rejected Claims 1-11 and 13-14 on the ground that the claims of the present invention are allegedly unpatenable over the claims of copending Application No. 10/522,208 (hereinafter "the '208 Application) or 10/586,188 (hereinafter "the '188 Application) in view of U.S. 5,051,407 or EP 536 402 and Brine et al. or Kato et al. as being barred by the non-statutory obviousness-type double patenting.

Applicants respectfully disagree. The '208 and the '188 Applications are directed to aza sugar derivatives having stereochemical configurations which are different from the compounds of formula (I) of the present invention. As argued above, there is nothing predictable about the biological activities of chiral compounds as can be seen in Kato et al. and the Butters et al. since one enantiomer of the aza sugar may be significantly more selective against a specific therapeutic activity than another enantiomer of that compound. Accordingly, the disclosure of activity and/or toxicity of one enantiomeric compound would not render obvious the activity and/or toxicity of the other enantiomer. Therefore, the claimed compounds of the current invention are unobvious and patentably distinct from those claimed in the '208 and the '188 Applications. As such, Applicants respectfully request the withdrawal of the obviousness-type double patenting rejection.

In the event that the Examiner maintains the rejection, Applicants note that the later filed case ('188 Application) has not even been examined, let alone issued as a patent nor have claims been allowed in this case nor in the '208 case. As none of these applications have allowable claims, Applicants respectfully submit that the obviousness-type double patenting rejection is premature and respectfully requested that this rejection be addressed upon allowance of claims in at least one of the applications.

9. CONCLUSION

In summary, compounds of different stereochemistry, particularly sugars and sugar

mimetics, may have completely different binding and/or biological activities as can be seen in Kato et al. and Butters et al. The teaching of one enantiomer as being biologically active would deter rather than motivate one skilled in the art to synthesize the other enantiomer, as there is no reason to expect the other compound to have the same activity, selectivity, or toxicity profile. Therefore, Appellants respectfully request that rejections of the pending claims be withdrawn.

As this response is filed within three months from the mailing date of the Non-final Office Action dated December 8, 2008, which response is due March 9, 2009, it is believed no fee is required. Should this be incorrect, the Commissioner is authorized to charge any additional fees, or credit any overpayment, to deposit account No. 50-4255.

Respectfully submitted,

Date March 9, 2009

By 

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